Complete Summary

GUIDELINE TITLE

Guidelines for using the QuantiFERON®-TB gold test for detecting mycobacterium tuberculosis infection, United States.

BIBLIOGRAPHIC SOURCE(S)

Centers for Disease Control and Prevention. Guidelines for using the QuantiFERON-TB Gold test for detecting Mycobacterium tuberculosis infection, United States. MMWR Recomm Rep 2005 Dec 16;54(RR-15):49-55. [179 references] PubMed

GUIDELINE STATUS

This is the current release of the guideline.

This guideline updates a previous version: Mazurek GH, Villarino ME. Guidelines for using the QuantiFERON-TB test for diagnosing latent Mycobacterium tuberculosis infection. Centers for Disease Control and Prevention. MMWR Recomm Rep 2003 Jan 31;52(RR-2):15-8.

COMPLETE SUMMARY CONTENT

SCOPE

DISEASE/CONDITION(S)

Latent Mycobacterium tuberculosis infection and tuberculosis disease

GUIDELINE CATEGORY

Diagnosis
Evaluation

CLINICAL SPECIALTY

Family Practice
Infectious Diseases
Internal Medicine
Pathology
Preventive Medicine
Pulmonary Medicine

INTENDED USERS

Clinical Laboratory Personnel
Health Care Providers
Public Health Departments

GUIDELINE OBJECTIVE(S)

- To provide interim guidance for use and interpretation of QuantiFERON®-TB Gold (QFT-G) testing for detecting latent Mycobacterium tuberculosis infection and tuberculosis (TB) disease
- To assist public health officials, clinicians, and laboratorians in their efforts to understand the use of QFT-G for TB control

TARGET POPULATION

- Persons at increased risk for latent Mycobacterium tuberculosis infection (e.g., recent immigrants, injection-drug users, and residents and employees of prisons and jails)
- Persons at low risk for latent M. tuberculosis infection but whose future activity might place them at increased risk (e.g., health-care workers and military personnel)
- Persons who are not considered to have an increased probability of M. tuberculosis infection but who require testing for other reasons

INTERVENTIONS AND PRACTICES CONSIDERED

1. QuantiFERON®-TB Gold test for diagnosis of latent Mycobacterium tuberculosis infection or tuberculosis disease
2. Medical evaluation (medical history, physical, chest radiograph, bacteriologic studies, serology for human immunodeficiency virus [HIV] testing, other tests where indicated)

MAJOR OUTCOMES CONSIDERED

- Detection of latent Mycobacterium tuberculosis infection and tuberculosis disease
- Predictive value of QuantiFERON®-TB Gold test (sensitivity, specificity of test)

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Searches of Electronic Databases
Searches of Unpublished Data

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

Not stated

NUMBER OF SOURCE DOCUMENTS

Not stated

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Not stated

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Not applicable

METHODS USED TO ANALYZE THE EVIDENCE

Review

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

Not stated

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

During July 11-12, 2005, the Centers for Disease Control and Prevention (CDC) convened a meeting in Atlanta, Georgia, of consultants and researchers with expertise in the field to review studies and assess experience with QuantiFERON®-TB Gold (QFT-G). Unpublished data from studies of QFT-G were considered in preparing these guidelines. Expert consultants, researchers, tuberculosis (TB) control public health practitioners, and representatives of the U.S. Food and Drug Administration (FDA), other federal agencies, and the manufacturer reviewed the evolving data on QFT-G. Data from ongoing studies evaluating QFT-G in U.S. Navy recruits, correctional facility inmates, persons with suspected TB disease, contacts of persons suspected to have TB disease, and health care workers were reviewed. For developing these guidelines, CDC

considered the scientific evidence and the opinions of the consultants. Their opinions did not represent endorsement from their organizations.

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Not applicable

COST ANALYSIS

A formal cost analysis was not performed and published cost analyses were not reviewed.

METHOD OF GUIDELINE VALIDATION

Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

Not stated

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

Indications for QuantiFERON®-TB Gold (QFT-G)

The US Food and Drug Administration (FDA) approved QFT-G as an in vitro diagnostic aid using peptide mixtures simulating early secretory antigenic target-6 (ESAT-6) and culture filtrate protein-10 (CFP-10) proteins to stimulate cells in heparinized whole blood. Detection of interferon-gamma (IFN-gamma) by enzyme-linked immunosorbent assay (ELISA) is used to identify in vitro responses to ESAT-6 and CFP-10 that are associated with Mycobacterium tuberculosis infection. From a medical and public health perspective, QFT-G testing is indicated for diagnosing infection with M. tuberculosis, including both tuberculosis (TB) disease and latent tuberculosis infection (LTBI). Whenever M. tuberculosis infection or disease is being diagnosed by any method, the optimal approach includes coordination with the local or regional public health TB control program.

How QFT-G Testing is Performed and Interpreted

Instructions for the QFT-G assay are in the package insert. Aliquots of heparinized whole blood are incubated with the test antigens for 16 to 24 hours. The blood must be incubated with the test antigens $\leq$12 hours after collection. Test kits include two mixtures of synthetic peptides representing ESAT-6 and CFP-10 as test antigens, phytohemaglutinin (a mitogen used as a positive assay control), and saline (used as a nil sample to measure the background level of IFN-gamma). After incubation, the concentration of IFN-gamma in the plasma is determined by ELISA by using the reagents included in the test kit. The amount of IFN-gamma released is determined by subtracting the amount in the nil from the amount in the ESAT-6, CFP-10, or mitogen-stimulated plasma. QFT-G test results can be

calculated by using software provided by the manufacturer. This report provides guidelines for interpreting test results (see table in the original guideline document titled "Interpretation of QFT-G results, from IFN-gamma concentrations in test samples"). Laboratory reports should include interpretation of QFT-G test results and indicate the concentration of IFN-gamma in each plasma sample.

Cautions and Limitations

Certain limitations of QFT-G are similar to those of the tuberculin skin tests (TST), but these limitations have not been studied extensively for QFT-G. Whereas the sensitivity of QFT-G for detecting M. tuberculosis infection in persons with untreated culture-confirmed TB is approximately 80% in published studies, its sensitivity for particular groups of TB patients (e.g., young children and immunocompromised patients) has not been determined.

QFT-G sensitivity for LTBI might be less than that of the TST, although the lack a confirmatory test makes this difficult to assess. Estimating the sensitivity of any indirect test for LTBI by testing patients who have TB disease might be inaccurate because of differences between these conditions. The ability of QFT-G to predict risk for LTBI progressing subsequently to TB disease has not been determined.

QFT-G, as with the TST, cannot differentiate infection associated with TB disease from LTBI. A diagnosis of LTBI requires that TB disease be excluded by medical evaluation, which should include checking for suggestive symptoms and signs, a chest radiograph, and, when indicated, examination of sputum or other clinical samples for the presence of M. tuberculosis.

Similar to any other diagnostic test, the predictive value of QFT-G results depends on the prevalence of M. tuberculosis infection in the population being tested. Each QFT-G result and its interpretation should be considered in conjunction with other epidemiologic, historic, physical, and diagnostic findings.

As with a negative TST result, negative QFT-G results should not be used alone to exclude M. tuberculosis infection in persons with symptoms or signs suggestive of TB disease. The presence of symptoms or signs suggestive of TB disease increases the likelihood that M. tuberculosis infection is present, and these circumstances decrease the predictive value of a negative QFT-G or TST result. Medical evaluation of such persons should include a history and physical examination, chest radiograph, bacteriologic studies, serology for human immunodeficiency virus (HIV), and, when indicated, other tests or studies.

The performance of QFT-G, in particular its sensitivity and its rate of indeterminate results, has not been determined in persons who, because of impaired immune function, are at increased risk for M. tuberculosis infection progressing to TB disease. Impaired immune function can be caused by HIV infection or acquired immunodeficiency syndrome (AIDS); current treatment with immunosuppressive drugs including high-dose corticosteroids, tumor necrosis factor-alpha (TNF-alpha) antagonists, and drugs used for managing organ transplantation; selected hematologic disorders (e.g., myeloproliferative disorders, leukemias, and lymphomas); specific malignancies (e.g., carcinoma of the head, neck, or lung); diabetes; silicosis; and chronic renal failure. Each of these conditions or treatments is known or suspected to decrease responsiveness

to the TST, and they also might decrease production of IFN-gamma in the QFTG assay. Consequently, as with a negative TST result, negative QFT-G results alone might not be sufficient to exclude M. tuberculosis infection in these persons.

Published data are relatively limited concerning the use of QFT-G among persons recently exposed to TB (e.g., contacts) and other populations at high risk for LTBI. No published data document the performance of QFT-G in children aged <17 years.

With any of the testing methods, persons who have a negative test result can still have LTBI. Those who have a negative result but who are likely to have LTBI and who are at greater risk for severe illness or poor outcomes if TB disease occurs might need treatment or closer monitoring for disease. Potential examples include close contacts who are aged <5 years, those who are immunocompromised because of HIV infection, or those who will undergo treatment with TNF-alpha antagonists (which increase the risk for progression from LTBI to TB disease).

QFT-G has practical limitations that include the need to draw blood and to ensure its receipt in a qualified laboratory in time for testing. The blood must be incubated with the test antigens $\leq$12 hours after collection, while the lymphocytes are viable. After the blood is incubated with antigens for 16-24 hours, plasma must be collected and either properly stored or tested promptly by ELISA. Collecting the required 5-mL blood sample from younger children might not be possible or acceptable.

Additional Considerations and Recommendations in the Use of QFT-G in Testing Programs

QFT-G can be used in all circumstances in which the TST is used, including contact investigations, evaluation of recent immigrants who have had Bacille Calmette-Guérin (BCG) vaccination, and TB screening of health-care workers and others undergoing serial evaluation for M. tuberculosis infection. QFT-G usually can be used in place of (and not in addition to) the TST.

A positive QFT-G result should prompt the same public health and medical interventions as a positive TST result. No reason exists to follow a positive QFT-G result with a TST. Persons who have a positive QFT-G result, regardless of symptoms or signs, should be evaluated for TB disease before LTBI is diagnosed. At a minimum, a chest radiograph should be examined for abnormalities consistent with TB disease. Additional medical evaluation would depend on clinical judgment on the basis of findings from history (including exposure to infectious TB), physical examination, and chest radiography. HIV counseling, testing, and referral is recommended because HIV infection increases the suspicion for TB and the urgency of treating LTBI. After TB has been excluded, treatment of LTBI should be considered.

The majority of healthy adults who have negative QFT-G results are unlikely to have M. tuberculosis infection and do not require further evaluation. However, for persons with recent contact with persons who have infectious TB, negative QFT-G results should be confirmed with a repeat test performed 8-10 weeks after the end of exposure, as is recommended for a negative TST result. Studies to determine the best time to retest contacts with negative QFT-G results have not

been reported. Until more information is available, the timing of QFT-G testing should be the same as that used for the TST.

When "window period" prophylaxis (i.e., treatment for presumed LTBI) is indicated for contacts aged <5 years or severely immunocompromised persons who are exposed to highly contagious TB, repeat testing for LTBI is recommended 8-10 weeks after contact has ended. With either TST or QFT-G, negative results of the test at the end of the window period should be interpreted by considering all available epidemiologic, historic, clinical, physical, and diagnostic information, including the findings for the other contacts in the investigation. A full course of treatment should be considered even with a negative result from either test at the end of the window period when the rate of M. tuberculosis transmission to other contacts was high or when a false-negative result is suspected because of a medical condition.

A greater rate of positive results has been reported with TST than with QFT-G in persons with and without recognized risks for M. tuberculosis infection, except for patients who have culture-confirmed TB disease. This tendency might be explained by either greater specificity with QFT-G, greater sensitivity with TST, or both. For this reason, all information must be considered when making treatment decisions for persons with increased risk for progression from LTBI to TB or in whom TB disease is associated with increased risk for severe illness or poor outcomes.

An indeterminate QFT-G result does not provide useful information regarding the likelihood of M. tuberculosis infection. The optimal follow-up of persons with indeterminate QFT-G results has not been determined. The options are to repeat QFT-G with a newly obtained blood specimen, administer a TST, or do neither. For persons with an increased likelihood of M. tuberculosis infection who have an indeterminate QFT-G result, administration of a second test, either QFT-G or TST, might be prudent. The potential for TST to cause boosting and the need for two-step testing in settings conducting serial testing should be considered. For persons who are unlikely to have M. tuberculosis infection, no further tests are necessary after an indeterminate QFT-G result. Laboratories should report the reason that the QFT-G result was indeterminate (e.g., high background levels of IFN-gamma in the nil sample or inadequate response to mitogen). In one report, inadequate response to mitogen was associated with immunosuppressive conditions.

As with the TST, if TB disease is suspected, additional diagnostic evaluations should be performed before or at the same time as the QFT-G and should not be delayed while awaiting QFT-G results. These evaluations should include chest radiography, bacteriologic studies, serology for HIV, and, as indicated by the illness, additional tests and studies. At present, as with the TST, the results of indirect tests for M. tuberculosis (e.g., QFT-G) usually would not influence the selection of additional tests and studies in such patients.

TB control programs can use QFT-G for investigating contacts of persons with potentially infectious TB disease. Because QFT-G does not require a second visit to complete, test results probably will be available from a greater percentage of contacts than would be available using TST. Because of its greater specificity, QFT-G is expected to indicate a smaller proportion of contacts as infected than the TST would indicate. Public health resources that previously were devoted to

completion of testing can instead be concentrated on full evaluation and complete treatment of contacts who have positive QFT-G results. In contrast to the TST, initial QFT-G testing of contacts will not boost subsequent test results, which avoids uncertainty about interpreting follow-up results. However, QFT-G might be less sensitive for LTBI than the TST, and its ability to predict subsequent development of TB disease is undetermined.

QFT-G might represent a cost-effective alternative to the TST in testing programs which are part of the TB infection control program in institutions such as health care settings, correctional facilities, or homeless shelters. In these settings, false-positive reactions to the TST pose a problem. This problem is compounded in settings with BCG-vaccinated persons born in countries where TB is prevalent. Follow-up visits for reading the TST also pose substantial operational challenges; the second visit for reading requires extra effort and leads to inefficiency. The greater specificity of the QFT-G and the requirement for only one visit are compelling advantages. General recommendations on the use of QFT-G as part of the infection control program in health-care settings have been included in the most recent revision of the TB infection control guidelines. In situations with serial testing for M. tuberculosis infection, initial two-step testing, which is necessary with the TST, is unnecessary with QFT-G and is not recommended.

TB control programs or institutions that elect to use QFT-G should consult and collaborate with laboratories in their system to ensure that specimens are properly obtained, handled, and processed prior to and after arrival in the laboratory. Information concerning the assay is in the package insert. Training of laboratory staff will be necessary. Certain facilities might elect to refer specimens for testing. The Clinical Laboratory Improvement Amendments (CLIA) regulations for quality systems of all phases of the total testing process (preanalytic, analytic, and post-analytic) and for general laboratory systems must be followed, including, but not limited to, the requirements for test system, equipment, instruments, reagents, materials and supplies, and the establishment or verification of performance specifications. In addition, under CLIA, documentation of all quality systems, including laboratory proficiency and staff competency, is required.

CLINICAL ALGORITHM(S)

None provided

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The type of evidence supporting the recommendations is not specifically stated.

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

- Compared with tuberculin skin testing (TST), QuantiFERON®-TB Gold (QFT-G) results are less subject to reader bias and error.

- QFT-G test results are available in <24 hours after testing, without the need for a second visit, whereas a TST requires a second visit to read results at 48-72 hours
- Targeted tuberculin testing programs may identify persons at increased risk for tuberculosis who will benefit from treatments for latent tuberculosis infection (LTBI).

POTENTIAL HARMS

- False-negative QFT-G test results
- Errors in collecting or transporting blood specimens or in running and interpreting the assay can decrease the accuracy of QFT-G.

QUALIFYING STATEMENTS

QUALIFYING STATEMENTS

Use of trade names and commercial sources is for identification only and does not imply endorsement by the United States Department of Health and Human Services.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

An implementation strategy was not provided.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Getting Better
Living with Illness

IOM DOMAIN

Effectiveness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

Centers for Disease Control and Prevention. Guidelines for using the QuantiFERON-TB Gold test for detecting Mycobacterium tuberculosis infection, United States. MMWR Recomm Rep 2005 Dec 16;54(RR-15):49-55. [179 references] PubMed

ADAPTATION

Not applicable: The guideline was not adapted from another source.

DATE RELEASED

2003 Jan 31 (revised 2005 Dec 16)

GUIDELINE DEVELOPER(S)

Centers for Disease Control and Prevention - Federal Government Agency [U.S.]

SOURCE(S) OF FUNDING

United States Government

GUIDELINE COMMITTEE

CDC Expert Consultation on QuantiFERON®-TB Gold

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FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

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GUIDELINE STATUS

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GUIDELINE AVAILABILITY

Electronic copies: Available from the Centers for Disease Control and Prevention (CDC) Web site:

- HTML Format
- Portable Document Format (PDF)

Print copies: Available from the Centers for Disease Control and Prevention, MMWR, Atlanta, GA 30333. Additional copies can be purchased from the Superintendent of Documents, U.S. Government Printing Office, Washington, DC 20402-9325; (202) 783-3238.

AVAILABILITY OF COMPANION DOCUMENTS

None available

PATIENT RESOURCES

None available

NGC STATUS

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